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## PERSPECTIVE

# COVID-19 vaccination in our transplant recipients: The time is now



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We are entering 2021 with an expanding and effective COVID-19 vaccine armamentarium. Recent interim results from COVID-19 vaccine trials, including more than 80,000 participants worldwide, demonstrate remarkable efficacy and low rate of serious adverse events. Based on experience with other vaccines in transplant recipients and knowing the risk of severe COVID-19 in this population, we believe that COVID-19 vaccines provide potential benefit with minimal risk. We strongly support and encourage COVID-19 vaccination of our transplant recipients.

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Although the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has highlighted many of the failings of our healthcare system and society, there has been one spectacular scientific achievement: within a year of the onset of the pandemic, we now have, and can administer, vaccines that effectively prevent serious coronavirus disease 2019 (COVID-19). The rapid development of these vaccines has built on substantive prior vaccine development focused on other pathogens such as severe acute respiratory syndrome, Middle East respiratory syndrome, and Ebola virus. Furthermore, the operational capacity to safely manufacture, deliver, and administer vaccinations has been honed over the past century. We are now poised to enter 2021 with an

effective vaccine armamentarium against COVID-19. However, the success of these efforts now hinges on widespread acceptance of the vaccines. Effective vaccine deployment to reach herd immunity and stop the pandemic relies on several factors: adequate supply, affordability and accessibility, secure cold chains to preserve the vaccine, and perhaps most importantly, obtaining the public's trust in the efficacy and safety of the vaccine. As clinicians who care for patients with chronic heart and lung diseases and organ transplants, we hold a unique position as a source of trusted information for our patients. In a pandemic marked by political divisions, misinformation exponentially amplified by social media, and an undercurrent of distrust of science, we believe it is critical that we engage our patients to encourage vaccination as soon as it is available, as endorsed by various transplant societies, including the International Society of Heart and Lung Transplantation, the American Society of Transplantation, and the American Society of Transplant Surgeons.<sup>1–3</sup>

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## The COVID-19 vaccine

Almost 80 vaccine candidates are undergoing development, are in clinical trials, or have been approved for administration in select countries.<sup>4</sup> Various novel and traditional mechanisms of action are employed, including the use of mRNA, replication-deficient adenovirus vectors, inactivated SARS-CoV-2 viruses, and protein subunits of SARS-CoV-2 (refer to Supplementary Table S1 available online at [www.jhltonline.org](http://www.jhltonline.org)). The major target for most vaccines is the viral spike protein and its receptor-binding domain interaction with human angiotensin-converting enzyme 2 receptor, the mechanism of viral entry into human epithelial cells.<sup>5</sup> Currently approved vaccines stimulate both B- and T-cell responses, engaging both humoral and cellular immune pathways.

Recent published interim results from COVID-19 vaccine trials include data from more than 80,000 participants enrolled globally with a median follow-up of 2 to 3 months.<sup>6–8</sup> Trials have included approximately 17% to 37% non-white participants, 47% to 61% women, and 20% to 30% participants with at least 1 medical comorbidity. Efficacy with symptomatic COVID-19 as the main end-point was ~95% for the mRNA vaccines and 70% for the adenovirus vector vaccine, far greater than the 50% threshold considered effective by the World Health Organization.<sup>9</sup> Importantly, efficacy against severe disease approached 100%; of the over 80,000 total enrolled participants, there were 42 cases of severe COVID-19, and of these, 41 occurred in participants who received the placebo. Asymptomatic infection also appeared reduced, which has potential implications for viral spread. Even more impressive, an effective immune response was observed as early as 10 to 14 days after the first of 2 vaccine doses.

Short-term adverse events were common and consisted mainly of local injection site reactions, although systemic effects such as fatigue, headache, and fever were reported, and typically resolved within 1 to 2 days. These are generally comparable with the adverse events seen with other commonly used vaccines for respiratory infections, such as influenza, pneumococcal disease, or whooping cough (pertussis). Both the frequency and severity of injection site reactions and systemic adverse events of COVID-19 vaccines were less in adults aged  $\geq 55$  years. Serious adverse events occurred in 0.5% to 1.5% of participants across the 3 reported trials, with similar distribution in both the vaccine and control arms. Concerns for vaccine-enhanced disease were not borne out in the current clinical trials, which included a subset of participants who were seropositive for SARS-CoV-2 at study entry, as well as those that developed COVID-19 in the vaccine arm.

## Vaccines in solid-organ transplant recipients

Transplant recipients were excluded from recent SARS-CoV-2 vaccine trials, so neither efficacy, durability, nor safety are known in this patient sub-population. However, as a transplant community, we have extensive experience with vaccine administration in stable transplant recipients, such as the influenza vaccine, although live

attenuated virus vaccines are generally contraindicated because of the theoretical risk of disseminated infection.<sup>10,11</sup>

The potential contraindication of live attenuated vaccines is not pertinent to SARS-CoV-2 as there are currently no SARS-CoV-2 vaccine platforms employing attenuated live virus approved for use or in Phase 3 trials; however, if they are developed and approved, they may be a valid approach for some non-immunocompromised pre-transplant candidates who are stable on the waitlist. Other concerns regarding the SARS-CoV-2 vaccines include lack of long-term safety data, potential reduction in efficacy in immunocompromised patients, unknown durability of the immune response, and potential for vaccine-associated allograft rejection. However, experience with the influenza vaccine and adjuvanted recombinant zoster vaccine can be extrapolated to the COVID-19 vaccine. First, unanticipated vaccine-associated adverse events to the allograft have not borne out, and vaccines are successfully administered to stable transplant recipients.<sup>11,12</sup> Second, neither the influenza vaccine nor the adjuvanted recombinant zoster vaccine has been associated with allograft rejection.<sup>11,12</sup> Finally, although the influenza vaccine may offer sub-optimal immunogenicity (improved with high-dose administration), the adjuvanted recombinant zoster vaccine in kidney transplant recipients demonstrates an adequate immune response and a lack of significant adverse events, including rejection.<sup>13,14</sup>

The novelty of the recently approved mRNA SARS-CoV-2 vaccines has prompted anxiety and misinformation fueled by social media. Use of synthetic mRNA for vaccines is new lipid nanoparticles transport mRNA into cells, enabling translation by human cellular ribosomes into SARS-CoV-2<sup>12</sup> spike proteins. However, concern for genetic manipulation is unwarranted: the mRNA is non-replicating, fails to integrate into the human genome, and is degraded after translation. Concerns for viral vector vaccines have focused on a runaway viral infection, especially when the host is immunocompromised. These concerns also have no scientific basis: the current adenoviral vaccines contain a non-replicating virus; this platform has been used for decades for gene therapy of rare diseases and cancer, although use for vaccination is newly approved. Other vaccines currently under investigation include inactivated virus and protein subunit vaccines; these vaccine platforms have been used in transplant recipients for other infections, including hepatitis A and B viruses, pertussis, and human papilloma virus.<sup>11</sup> As transplant clinicians, we should appropriately educate our patients regarding the significant vaccine-related benefits based on the scientific mechanisms and clinical trial findings rather than leave them to interpret the often questionable information on social media. Vaccine acceptance can be maximized by providing accessible educational material for patients and their families, virtual seminars, and one-on-one conversations in which specific fears and questions can be discussed.

## The time is now

Although transplant recipients have yet to be studied in SARS-CoV-2 vaccine Phase 3 trials, the benefits in non-

transplant recipients are clear, as are the risks our transplant recipients face from COVID-19. In a recent analysis, transplant recipients with COVID-19 had a 30% increased risk of death or mechanical ventilation compared with matched controls.<sup>15</sup> The emerging studies on SARS-CoV-2 vaccines indicate that they are safe and effective, and our experience with prior vaccines in stable transplant recipients suggests that the COVID-19 vaccines will also be safe and effective in transplant recipients. Of course, we need to enroll transplant recipients in observational studies, registries, and clinical trials to assess both vaccine immunogenicity, including durability of humoral and cell-mediated immunologic response, and vaccine side effects, including rejection and allosensitization. In addition, what we learn now will help us navigate the next global infectious threat. Until this information becomes available, we believe that the SARS-CoV-2 vaccines provide potential benefit and minimal risk to stable transplant recipients, particularly when this pandemic is surging in many parts of the globe.

William Osler once said, "Medicine is a science of uncertainty and an art of probability," and we must accept the uncertainty as we weigh the probabilities of SARS-CoV-2 infection and the vaccine. Our transplant recipients are far more likely to suffer a severe outcome from COVID-19 than from the vaccine. Therefore, as clinicians who strive to optimize the health and wellness of our patients, we believe SARS-CoV-2 vaccination is essential and strongly support and encourage vaccination of our transplanted recipients.

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## Supplementary materials

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## Supplementary data

Supplementary data associated with this article can be found in the online version at [www.jhltonline.org/](http://www.jhltonline.org/).

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